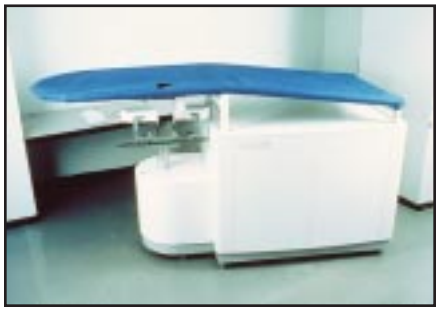
HEALTH AND MEDICAL TECHNOLOGIES

Think of BMDO technology transfer the next time you

- Read a newspaper article about someone who is surviving breast or prostate cancer.
- Get word that a friend has sustained a disabling back injury.
- Hear of a hospital patient who is being treated for throat cancer.
- View a television program featuring a medical research facility where cutting-edge techniques and technologies are being developed.

MICROWAVES ZERO IN ON BREAST TUMORS

Microwave technology produces safe and controlled deep heat to treat patients with breast cancer, prostate cancer, and other life-threatening diseases.



■ The Celsion breast cancer treatment system (pictured above) can increase the effectiveness of breast-conserving cancer treatments, such as lumpectomy, radiation therapy, and chemotherapy.

■ Celsion's deep cancer treatment system (pictured above), currently being developed, will target generally inoperable tumors deep within the body.

This year, the American Cancer Society estimates that 178,000 American women will be diagnosed with breast cancer and roughly 43,000 will die from the disease. Many of these lives may someday be saved by treating the tumor with heat, a technique better known as hyperthermia. But in targeting tumors deep inside the body, conventional heat treatments can create hot spots that burn the skin or surrounding healthy tissue.

Fortunately, Celsion Corporation (Columbia, MD), formerly Cheung Laboratories, has found a way to solve this problem. The company has developed a breast cancer treatment system, called Microfocus 1000™, that uses deep, focused heat to eradicate cancerous tumors—without overheating surrounding tissue. Concurrently heating and applying either radiation or chemotherapy shrinks tumors up to twice as fast as subjecting them only to conventional treatments.

Furthermore, recent preclinical tests conducted by Massachusetts General Hospital in Boston showed that heat alone can eradicate tumors effectively. This approach could eventually eliminate the need for radiation-based treatments, which can cause nausea, radiation burns, hair loss, and even secondary tumors. Later this year, Celsion plans to use this method to eradicate breast tumors in patients at several hospitals.

Cancel out radiation. Adaptive phased array (APA) software is key to the precision of Microfocus 1000. APA algorithms were initially developed by MIT Lincoln Laboratory (Lexington, MA) to locate airborne vehicles, such as cruise missiles, from BMDO space-based radar platforms. The algorithms were designed to overcome enemy jamming by removing the electronic noise from the radiation signals coming back to the radar. Since then, the same APA techniques have been applied in tumor eradication. In this application, they cancel out the radiation signals hitting healthy tissue, allowing the microwaves to be more precisely focused on the tumor.

APA technology gives doctors a new level of control in the heat treatment of tumors. "Hyperthermia systems have been around for a long time and, for the most part, they have been ineffective in reaching the tumor site with concentrated microwaves," says John Mon, Celsion's general manager. "APA technology focuses microwaves right on the tumor, killing the cancer cells more directly.

Because of its greater precision, it doesn't produce hot spots on surrounding tissue, so the patient feels no pain during or after the procedure."

Celsion is making significant progress in bringing Microfocus 1000 technology to the market. In September 1997, the company received premarket approval from the U.S. Food and Drug Administration to incorporate APA technology into its already-approved Microfocus 1000, making the device immediately available for medical use. Celsion also has obtained an exclusive license for the commercial use of MIT's APA technology. Several hospitals have successfully used Celsion's prototypes in animal models, paving the way for the treatment of human patients.

Intravenous drug delivery. In a sponsored research alliance with Duke University Medical Center in Durham, North Carolina, Celsion will use APA technology to develop a new family of heat-activated targeted drug delivery, gene therapy, and anti-angiogenesis systems. The first major emphasis of the alliance is the development of heat-sensitive lipid-based microcarriers, which encapsulate drugs for intravenous delivery. Upon reaching the tumor where the focused heat is applied, the microcarrier is designed to undergo a physical change that leads to a release of the entire encapsulated drug content within a few minutes. This approach concentrates the toxic effects of the drug at the site by 50 times that of current liposome therapies, with minimal side effects.

Celsion is also developing APA-based devices for treating prostate cancer and other life-threatening diseases. The APA prostate cancer treatment system will increase the effectiveness of radiation therapy by about a factor of two without any added side effects. Preclinical testing is currently being conducted in Celsion's laboratory with a prototype. This year, Celsion will ship the prototype to the University of California at San Francisco where preclinical studies using animals without tumors will be conducted.

A deep cancer treatment system also uses the focused-heating APA method, safely eradicating tumors far inside the body without harming surrounding tissue. The system is designed to target tumors in the liver, rectum, cervix, pancreas, lung, and other areas deep within the torso. The prototype, which is currently being developed, will be used in clinical trials at both Duke University Medical Center and Northwestern Memorial Hospital in Chicago, Illinois.

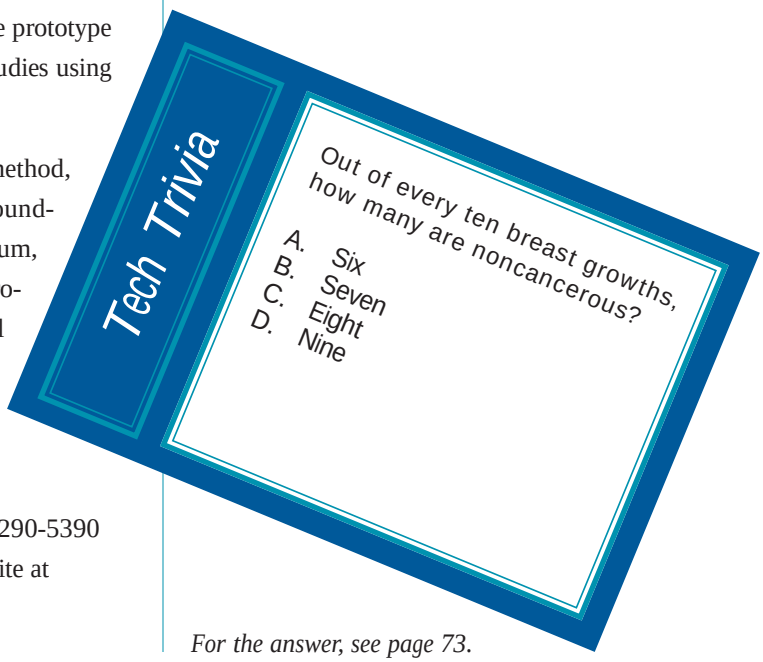
■ For more information, contact John Mon via telephone at (410) 290-5390 or via E-mail at celsion@aol.com. You can also visit Celsion's Web site at http://www.celsion.com.

What Does It Mean to You?

Celsion's new technology offers more accurate delivery of thermal therapy for eradicating cancerous breast tumors, helping to widen the range of treatment choices for women with these disorders.

What Does It Mean to Our Nation?

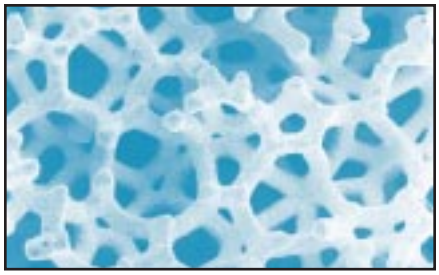
Celsion's Microfocus 1000 can be used as part of the thousands of breast-conserving surgeries that are performed each year, reducing the complications and risks associated with these procedures.



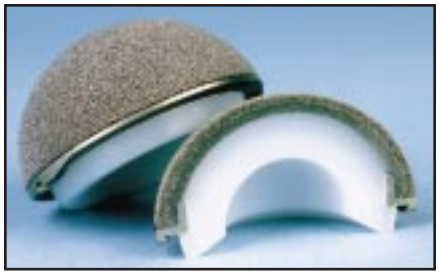
For the answer, see page 73.

IMPLANTS MEAN MORE SUPPORT FOR WEAKENED SPINES

A synthetic cellular material once used to insulate rocket nozzles is now restoring mobility and comfort to the lives of spinal implant patients.



■ Hedrocel® cellular materials (pictured above) are readily compatible with natural bone.



■ Pictured above is the Hedrocel® Acetabular Cup, a commercially available device used in total hip replacements for patients suffering from hip arthritis.

The human spine may be resilient, but it is not impervious to harm. Damage can result from trauma when the tissues between the vertebrae of the spine are compressed, which is what happened to actor Christopher Reeve during his tragic horseback riding accident. Less obvious damage can result from bone diseases such as osteoporosis and arthritis, which gradually destroy spinal bone mass during the aging process.

Ultramet, Inc. (Pacoima, CA), has developed a synthetic cellular biomaterial that in some cases of trauma and disease could help shore up the spine, preventing further injury. With its relatively high strength and porous structure, the biomaterial can act as a biocompatible replacement for damaged vertebral bodies and as a facilitator for spine fusion. In either case, it can greatly reduce the pain typically associated with bone and between-the-bone tissue loss, thus improving the quality of life for those with debilitating spinal problems caused by accidents or bone degeneration diseases.

Similar to cork. The biomaterial is an open-celled lattice that mimics the properties of, and is compatible with, bone. It appears similar in structure to natural materials such as coral and cork, but it is made stronger with tantalum—the most corrosion-resistant, biologically acceptable metal available today. The biomaterial was derived from a BMDO SBIR project to develop synthetic cellular foams that could serve both as insulators and kinetic energy absorbers. BMDO funded the materials development to produce insulation technology for components inside rocket nozzles.

Implex Corporation (Allendale, NJ) has licensed and further developed this biomaterial for use in many musculoskeletal applications, including the human spine. Called Hedrocel®, the biomaterial can be used for permanent spinal applications. For example, it can be implanted between two vertebrae, providing immediate structural support for the spinal column. Left alone, it allows bone from the vertebrae above and below to gradually infiltrate its pores. This bone will gradually join and form a true bony fusion across the whole joint. This fusion reduces the possibility of pain from compressed spinal nerves.

The company considers Hedrocel to be a platform technology whose porosity and flexibility are well suited for spinal and other human body applications.

"The biomaterial's uniquely shaped, interconnecting pores result in a bulk volume porosity of greater than 80 percent," says Robert Cohen, Implex Corporation's vice president of product development. "Because of this high porosity, it has more room for bone to grow into the material, providing greater biological stability than conventional implant materials." Mr. Cohen adds that the material's flexibility "more closely resembles that of bone." Any spinal replacement material that is too stiff could cause undue load transmission to the spine because of the difference in flexibility characteristics. The bone will then remodel abnormally, creating another surgical challenge in the future.

Hedrocel implants can help patients with conditions such as osteoporosis when doctors feel that structural support is the most preferable option. According to the National Osteoporosis Foundation, osteoporosis is a major public health threat for more than 28 million Americans, 80 percent of whom are women. In the United States today, 10 million individuals already have the disease and 18 million more have low bone mass, placing them at increased risk for osteoporosis. The estimated national direct expenditures (hospitals and nursing homes) for osteoporotic and associated fractures is $13.8 billion ($38 million each day), and the cost is rising.

Successful trials. Implex's Hedrocel vertebral body replacement implants have been successfully used in 12 patients in Europe. Some patients had a lumbar (lower back) bone replaced, while others had a cervical (neck) bone replaced. In Europe and the United States, the Hedrocel cervical spacer implants have also successfully been used for cervical fusion by replacing the disc to allow the adjacent bones to grow together. Implex reports that the clinical results to date are positive and compelling.

Other Hedrocel products for joint replacement and fusion are emerging. In mid-1997, the company received U.S. Food and Drug Administration acceptance for a Hedrocel socket-side hip implant, which can be used in total replacements for patients with hip arthritis. These implants are currently being marketed. In addition, Implex is investigating the use of Hedrocel in cases requiring the fusion of joints in the human body; typically this procedure gives the patient a better quality of life after an accident or condition that makes bending a finger, wrist, or ankle too painful.

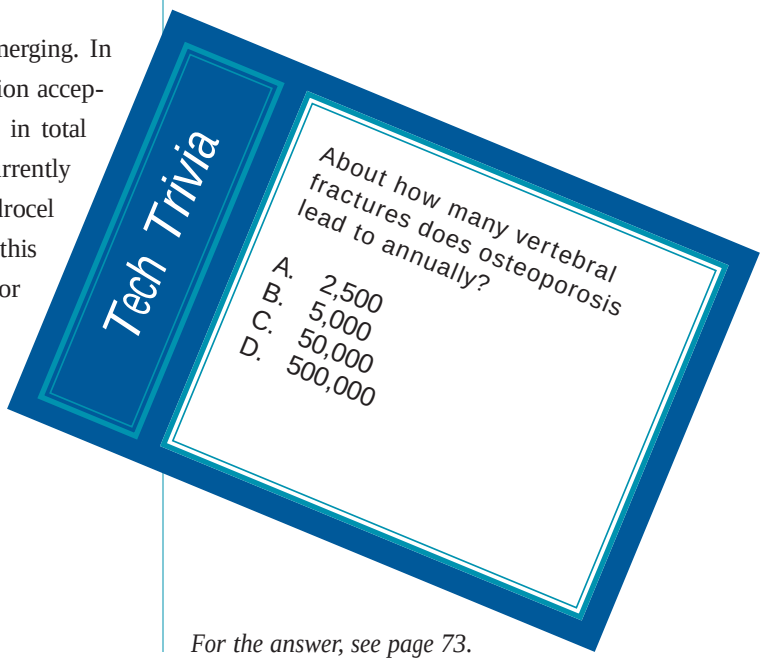
■ For more information, contact Robert Cohen via telephone at (201) 818-1800 or via E-mail at robert.cohen@implex.com.

What Does It Mean to You?

Spinal implants can help relieve pain in persons suffering from degenerative spinal disease and may soon help restore motion to arthritic ball-and-socket joints in the hips.

What Does It Mean to Our Nation?

Spinal implants can help improve the quality of life for the 25 million Americans who either have or are at high risk for osteoporosis, which results in annual estimated costs of more than $10 billion for direct medical treatment.



For the answer, see page 73.

OPTICAL BIOPSY SHINES NEW LIGHT ON CANCER

A new laser-based biopsy procedure can diagnose cancer of the esophagus almost instantaneously without the pain of tissue sampling.

■ Instead of using a pincer-tipped cable (pictured in foreground), researchers have developed a new, laser-based, nonsurgical method to diagnose certain cancers, such as esophageal cancer.

It was 18 years ago that retired engineer Melvin Francis first noticed something was wrong. "I had burning sensations in my throat," he recalls. With the aid of an endoscope, Dr. Bergein Overholt diagnosed the problem as Barrett's esophagus, a precancerous condition in which the lining of the esophagus is severely irritated.

After the surgery to remove the precancerous abnormalities, Dr. Overholt began a series of biopsies to analyze the tissue in Francis' esophagus. These procedures removed samples of sensitive esophageal lining and were quite painful, according to Francis. And obtaining the results took days, producing many anxious moments for him and his family. This scenario is typical for many others diagnosed with esophageal cancer.

Working with Dr. Overholt and research scientist Dr. Masoud Panjehpour, Dr. Tuan Vo-Dinh of Oak Ridge National Laboratory (ORNL; Oak Ridge, TN) has developed a new, fast, noninvasive fiber-optic probe to detect cancer of the esophagus. The probe induces and detects fluorescence of the tissue and can determine whether or not suspicious lesions are cancerous. It yields diagnoses noninvasively, without biting into tissue the way a conventional biopsy does. And it produces diagnoses fast, without the delay of sending away samples for evaluation and waiting for a pathologist's report.

Tissue's glow analyzed. The probe substitutes light for the scalpel of surgical biopsy. Using the body's own light emission in reaction to certain wavelengths of laser light, a spectrometer, an instrument for visualizing light emitted from an organ's tissue, can detect unique fluorescent signals. As demonstrated in studies conducted by the probe's developers, this activity can reveal cancerous hot spots without removing tissue. Dr. Vo-Dinh first realized the potential of this technology while using lasers to conduct data storage experiments for BMDO and environmental monitoring studies for the Department of Energy. BMDO's experiments focused on a new technology for optically storing vast amounts of computer data, called surface-enhanced Raman optical data storage.

The optical probe technology could change the course of medicine in diagnosing certain tumors. "Optical biopsies are noninvasive and fast because no tissue is removed and the diagnosis can be made almost immediately," says Dr. Vo-Dinh, ORNL's division leader for the Life Sciences Group. "Conventional tumor

biopsy requires the use of a pincer-tipped cable to physically remove tissue for analysis. Such a procedure entails recovery time for patients and an expensive, time-consuming laboratory analysis to determine malignancy."

In the new method, instead of the biopsy "pincer" cable, a fiber-optic cable is inserted in the biopsy channel of an endoscope. Laser light is directed through the cable's optical fibers onto the tissue. The tissue absorbs the laser light and, depending on the light's wavelength, re-emits it as a fluorescent "glow," which is spectrally analyzed. Using a special data analysis method, the researchers discovered that the spectral "fingerprint" of a malignant tumor can be distinguished from that of a noncancerous tumor.

Highly accurate. The probe technology was put to the test against standard mechanical biopsies at the Thompson Cancer Survival Center in Knoxville, Tennessee. In a research investigation involving 100 patients, the technology accurately diagnosed 98 percent of all esophageal tumors. In fact, in one case, the mechanical biopsy was normal, but the optical biopsy detected a malignancy.

The technology has been licensed to Venture Alliance (Knoxville, TN), a venture development company that invests in and manages early-stage technologies, particularly those for the medical industry. Venture Alliance formed Optical Biopsy Technologies, L.L.C., to further develop and commercialize the optical probe technology. Working with the U.S. Food and Drug Administration, Optical Biopsy Technologies has completed pilot clinical studies for both gastrointestinal (GI) and cervical applications and has received an investigational device exemption for the GI application. The company is currently seeking additional investors.

Vo-Dinh's BMDO-funded research and development in optical data storage also led to the development of a surface-enhanced Raman gene probe (SERGen). The probe requires no radioactive tags or special fluorescing dyes and cuts gene identification time drastically, from as many as 16 hours to a matter of minutes. Because of its speed and sensitivity, the probe could prove useful in many areas.

For example, in our era of increasing antibiotic resistance, SERGen may prove a boon to doctors who want to quickly identify resistant organisms. Doctors can then prescribe the proper medication and avoid a wasted course of ineffective antibiotics. SERGen also could offer a drastic improvement in the methodology used for gene sequencing and identification, such as that being applied in the Human Genome Project.

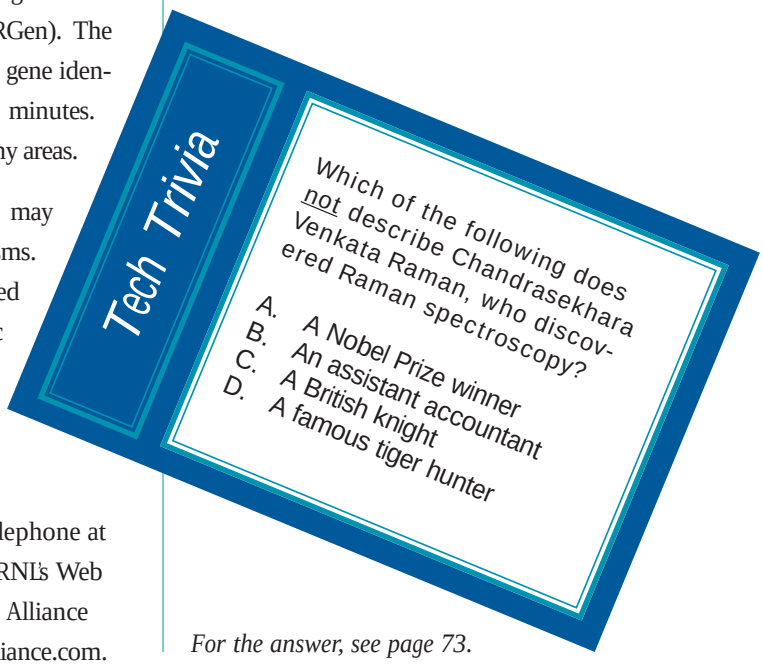
■ For more information, contact Dr. Tuan Vo-Dinh of ORNL via telephone at (423) 574-6249 or via E-mail at tvo@ornl.gov. You can also visit ORNL's Web site at http://www.ornl.gov. Or, contact Robert Lundgren of Venture Alliance via telephone at (423) 523-2346 or via E-mail at lundgren@venturealliance.com.

What Does It Mean to You?

Optical biopsy can help to diagnose cancers earlier and before they have had a chance to spread, and can also alert the clinician to precancerous conditions that can thereafter be carefully monitored.

What Does It Mean to Our Nation?

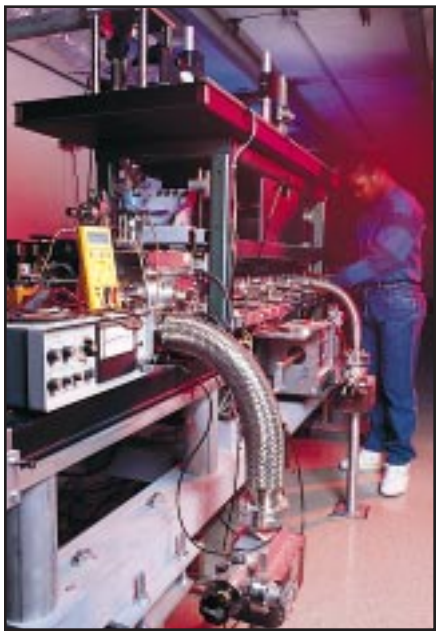
Optical biopsy is an emerging technique that can be performed at a cost 10 times cheaper than conventional biopsies, reducing the cost of specialized medical care for cancer patients.



For the answer, see page 73.

A NEW DAY DAWNS FOR REVITALIZED LASER

Once limited to the physics laboratory, the free-electron laser has found a new life as a unique tool for medical and industrial research.



■ A laser technician works on Vanderbilt University's free-electron laser (pictured above), which has provided major breakthroughs in mammography and neurosurgery.

In the early years of medical laser research, doctors used single-wavelength lasers with limited dynamic properties. When the free-electron laser (FEL) was developed, it offered short pulses, high peak power, and a greater range of wavelengths. Not surprisingly, this innovation yielded a host of advances in the medical field. Vanderbilt University (Nashville, TN) is a nexus of these advances.

During the late 1980s, Vanderbilt was one of several centers of excellence to receive funding through BMDO's Medical Free-Electron Laser (MFEL) program. The U.S. Congress conceived the MFEL program as a means to leverage and transfer technology from the military's laser research program to the medical community. Since then, the advanced capabilities of the FEL have benefited both clinicians and basic scientists, enabling dramatic progress in laser medicine, materials science, and a host of other specialties. Many research centers translated the FEL's advances into procedures that now use portable lasers such as the neodynium:YAG.

Underground vault. Vanderbilt, however, has taken a novel approach, building a multidisciplinary facility around its 75-foot-long FEL. Housed in the basement of the W.M. Keck Free-Electron Laser Center, the enormous laser is encased in a 13,000 ft^2 vault of thick concrete. A series of tubes and mirrors route the beam to the second floor of the center, which houses the FEL control room, five laser target rooms, two experimental surgical suites, and supporting biology and electronics laboratories. The arrangement encourages a free exchange of ideas among surgeons, clinicians, physicists, and biologists who are the primary beneficiaries of the FEL's presence.

The FEL program at Vanderbilt won an initial grant from the Office of Naval Research (ONR) and BMDO (then the Strategic Defense Initiative Organization) in 1987. The W.M. Keck Foundation contributed funds in 1993 to help expand the FEL facility, and ONR added more funding in 1996. Today, Vanderbilt scientists are testing the laser for a variety of clinical purposes.

For example, one primary task is generating monochromatic x-rays for mammography. According to breast cancer specialist Dr. Frank Carroll, these FEL-generated beams potentially will make tumor images "stand out like headlights," greatly enhancing a mammographer's ability to detect cancer. In addi-

tion to better image clarity, this method exposes the patient to ten times less radiation than conventional mammography. In the future, work with Los Alamos, Lawrence Livermore, and Oak Ridge National Laboratories is expected to yield a new imaging technique that uses 100 times less radiation than current x-ray technology.

Tumors beware! Vanderbilt neurosurgeon Dr. Michael Copeland says that the FEL is the best answer yet for expanding the role of lasers in neurosurgery. Carbon dioxide and erbium:YAG lasers cause too much thermal damage to be used extensively in neurosurgery, but the more precise control and tunability of the FEL may change the way surgeons regard lasers for this specialty. Deep-seated tumors previously considered inoperable may be treated more effectively with the infrared beams of the FEL. Pending approval by the U.S. Food and Drug Administration by the end of 1998, Dr. Copeland expects to perform the first human neurosurgery using the FEL.

In addition to laser medicine, the FEL can open windows into the materials world of such manmade structures as solar cells, electronic devices, and biosensors. Amorphous silicon solar cells can be bombarded with intense light to examine how and why these cells wear out over time. In the same way that the FEL interacts with the individual atoms of DNA to give molecular information, the atoms in a semiconductor can be manipulated to yield information about its electrical properties. Even the interface between living and nonliving structures can be explored to create biosensors, which are implanted silicon chips that can react to glucose, for instance, and deliver insulin in response.

In electronics, diamond substrates are another interesting topic for FEL users. For many years, researchers have worked to harness the excellent properties of diamond to make faster transistors. A problem with modifying diamond surfaces, however, is the destructive thermal heating associated with conventional processing methods. The FEL's precise tuning, short pulses, and high power can help scientists cut through diamond without collateral heat damage and without disrupting the orderly crystalline lattice that makes diamond so desirable.

The FEL's potential ultimately will be fulfilled not by the nature of the technology, but rather by the vision of those who use it. By cooperating and exploring new ideas, Vanderbilt's FEL researchers will likely produce even more exciting developments in the future.

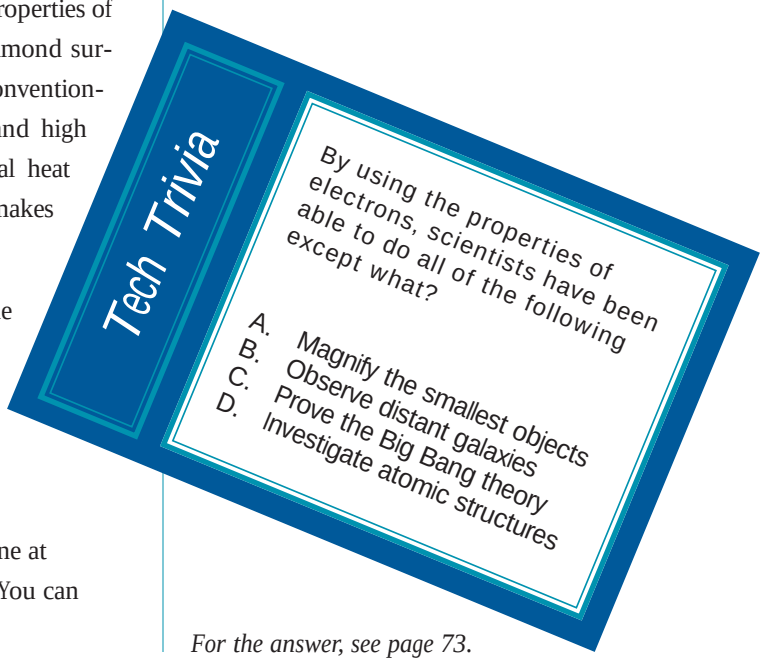
■ For more information, contact Dr. Glenn S. Edwards via telephone at (615) 343-6146 or via E-mail at edwardg1@ctrvax.vanderbilt.edu. You can also visit Vanderbilt's Web site at http://www.vanderbilt.edu.

What Does It Mean to You?

Free-electron lasers may allow surgeons to cut with far less damage to surrounding tissue and mammographers to obtain the clearest images to detect cancer, leading to better health care procedures.

What Does It Mean to Our Nation?

Free-electron lasers can address the challenges of human disease and disorders through new treatment techniques, potentially improving patient care and reducing medical costs.



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